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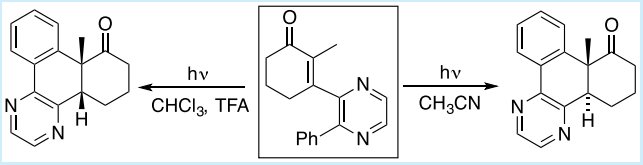
Stereodivergent Photoelectrocyclization Reactions of Bis-aryl Cycloalkenones: Intercepting Photoelectrocyclization Intermediates with Acid

Xuchen Zhao, Changqing Song, and Jon D. Rainier*

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, United States

Supporting Information

ABSTRACT: Described here are tandem photoelectrocyclization and [1,5]-hydride shift reactions of heteroaryl-containing bis-aryl cyclohexenone derivatives that give heteroaryl-substituted dihydrophenanthrenes. This Letter demonstrates that electrocyclization intermediates can be trapped with acid when the [1,5]-hydride shift is relatively slow. From a practical perspective, the observation that the acid-mediated reaction gives a divergent stereochemical outcome when compared with the reaction run under neutral conditions makes these transformations powerful.

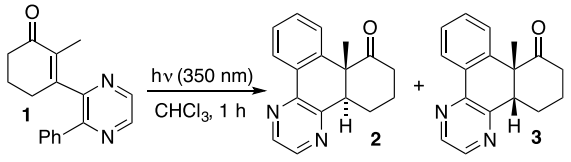


As first reported by Horgan and Morgan in 1973, the treatment of conjugated biaryl alkenes with UV light leads to the stereoselective generation of dihydrophenanthrenes.[1] Subsequent to their initial report, Horgan and Morgan's photoelectrocyclization reaction received considerable attention from researchers around the globe, and, as a consequence, a considerable amount of mechanistic insight was uncovered.[2] From these studies, it has been established that (a) bond formation involves a sequential 6π conrotatory electrocyclization, followed by a thermally allowed [1,5]-hydride shift;[3,4] (b) the substrates do not react under thermal condition;[5] and (c) the reaction generally proceeds through a singlet excited state.[6]

In contrast with all of the mechanistic information that has been uncovered, neither the scope of the photoelectrocyclization reaction of bis-aryl alkenes nor the use of the reaction in the synthesis of more complex substrates has been studied in any significant detail.[2,5,7] With this in mind and with an interest in using dihydrophenanthrenes in the synthesis of interesting targets including natural and non-natural products, we set out to change this.[8−10] As a demonstration of the potential of the electrocyclization process, we recently described the tandem photoelectrocyclization and [1,5]-hydride shift of a series of conjugated biphenyldihydropyridones, giving trans-fused dihydrophenanthrenes.[11] Outlined here is a follow up on these studies with an investigation of heteroaromatic substrates as a means of synthesizing diterpene natural products that have shown the ability to inhibit virulence.[12] Our interest in heteroaromatic substrates comes from both a curiosity about the properties of the dihydrophenanthrene products and the possibility of carrying out chemoselective dearomatization reactions subsequent to the photoelectrocyclization.[13] In light of these interests, we elected to initially examine conjugated pyrazines.

We began our efforts with conjugated phenylpyrazine cyclohexenone **1** that comes from sequential Suzuki−Miyaura coupling reactions (Table 1).[14,15] Whereas we were pleased to isolate quaternary substituted dihydrophenanthrenes when **1** was exposed to 350 nm light, we were surprised that the reaction not only gave the expected *trans*-fused product **2** but also gave *cis* diastereomer **3** (entries 1 and 2).

Table 1. Phenyl Pyrazine Photoelectrocyclizations



entry	additive	solvent	2:3[a]	conversion (%)[b]
1	none	$CHCl_3$	1:2	93
2	none	$CDCl_3$	1:4[c]	50
3	none	C_6D_6	>20:1	94
4	none	CD_3OD	12:1	65
5	none	CD_3CN	>20:1	85
6	none	$CDCl_3$[d]	>20:1	80
7	NEt_3	$CDCl_3$	>20:1	86
8	HCl (0.5 equiv)	$CDCl_3$	1:2	50
9	HCl (2 equiv)	$CDCl_3$	1:3	40
10	TFA (2 equiv)	$CDCl_3$	<1:20	65

[a]Ratio was determined by ^{1}H NMR integration of the benzylic signals. [b]Conversions were determined by ^{1}H NMR using 2,4,6-trimethoxybenzeneas an internal standard. [c]Reaction was stopped after 15 min. [d]$CDCl_3$ was neutralized prior to its use.

It turns out that the transformation to **3** was dependent on the solvent employed in the reaction. In contrast with the

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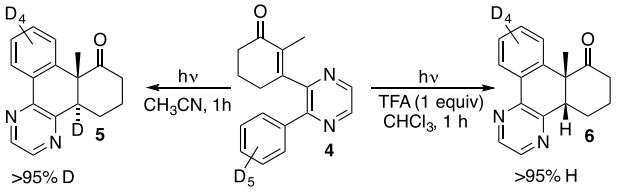
result with $CHCl_3$, *trans*-**2** was the nearly exclusive product when the reaction was run in deuterated benzene, methanol, or acetonitrile (entries 3−5). With an interest in utilizing related derivatives as precursors to interesting alkaloids,[16] we set out to determine whether we could find conditions to selectively generate **3**. As far as the result with $CHCl_3$ was concerned, we reasoned that the presence of HCl in the $CHCl_3$ might be responsible for its generation. Consistent with this hypothesis were experiments showing that the use of neutralized $CHCl_3$ led to the isolation of **2** as the sole product (entries 6 and 7). In contrast, the addition of larger quantities of HCl proved detrimental. That is, the addition of exogenous HCl to the photoelectrocyclization reaction led to both a slower reaction and relatively less *cis* product when compared with running the reaction in $CHCl_3$ or $CDCl_3$ that had not been neutralized (compare entries 1, 2, 8, and 9). After considerable experimentation, we ultimately found that the use of a weaker acid, namely TFA, nearly exclusively gave **3** (entry 10). In addition to optimizing conditions for its formation, we were curious about whether **3** came from the isomerization of **2** during the reaction. When **2** was exposed to TFA, no equilibration occurred in either the presence or the absence of light.

Having established conditions to generate either **2** or **3**, we next set out to determine the source of the benzylic proton in both products. To do this, we examined the photoelectrocyclization of penta-deuterated cyclization precursor **4** (Scheme 1). Subjecting **4** to 350 nm light in the presence of TFA

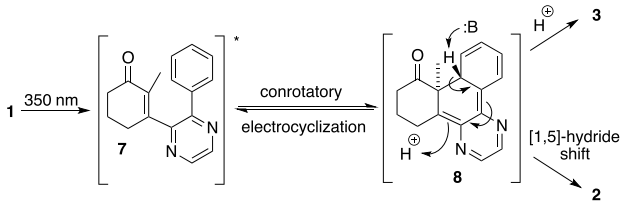
Scheme 1. Labeled Pyrazine Photoelectrocyclizations



resulted in *cis*-dihydrophenanthrene **6** with no label at the benzylic position. In contrast, when **4** was exposed to 350 nm light in CH_3CN in the absence of acid, we isolated **5**, having >95% deuterium incorporation at the benzylic position. These results confirm that protonation rather than a [1,5]-hydride shift of the photoelectrocyclization intermediate leads to the *cis*-dihydrophenanthrene.

On the basis of the information presented above, we propose the mechanism outlined in Scheme 2. We believe that both **2** and **3** result from the excitation of **1** and the generation of the corresponding excited state **7**. Because the use of triplet sensitizers and quenchers has not been informative to date, we do not currently know whether the reaction involves a singlet or a triplet excited state. Our labeling experiments are

Scheme 2. Proposed Mechanism



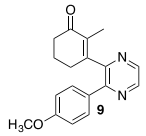
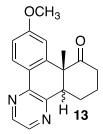
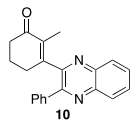
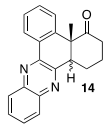
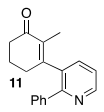
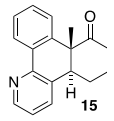
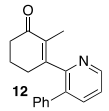
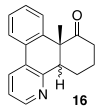
consistent with a subsequent six-electron conrotatory electrocyclization providing intermediate **8**. Apparently, the [1,5]-hydride shift from **8** is relatively slow, enabling other events like protonation to intervene. Under acidic conditions, stereoselective protonation, as depicted, provides **3**. In the absence of acid, the normal suprafacial [1,5]-hydride shift leads to **2**.

There are several unique features of the **1** to **2** or **3** transformations. To the best of our knowledge, **2** represents the first photoelectrocyclization precursor of the bis-aryl vinyl class of substrates whose photoelectrocyclization intermediate can be manipulated nonoxidatively. As was previously mentioned, this manipulation leads to a completely divergent stereochemical outcome that makes these transformations not only mechanistically interesting but also synthetically powerful.

In an effort to ascertain whether other heteroaromatics might be susceptible to the generation of cis products when exposed to acid, we examined the impact of TFA on the photoelectrocyclization of other nitrogen heterocycles. It was interesting that both the position and the number of nitrogen atoms were important in the protonation reaction (Table 2).

Table 2. Heteroaromatic Photoelectrocyclizations

bis-arylcyclohexenone $\xrightarrow[\text{conditions}]{h\nu\ (350\ nm)}$ dihydrophenanthrene(s)

entry	enone	cond.[a]	product	yield	*cis:trans*
1		A		85%	>20:1
2	**9**	B	**13**	95%	<1:20
3		A		82%	>20:1
4	**10**	B	**14**	89%[b]	<1:20
5		A or B		90%	<1:20
6		A		86%	1.6:1
7	**12**	B	**16**	91%	<1:20

[a]**A**: $CHCl_3$, TFA (1 equiv). **B**: CH_3CN. [b]Reaction was run on a 1 mmol scale.

The reactivities of substituted pyrazine **9** and quinoxaline **10** were essentially identical to the behavior of **1**. That is, both gave exclusively *trans*-fused products when subjected to light in the absence of acid while resulting in cis product when TFA was added to the reaction mixture (entries 1−4). In contrast with these results, the photoelectrocyclization of conjugated pyridine **11** gave exclusively *trans* product **15** regardless of whether acid was present (entry 5). It was interesting that the regioisomeric pyridine **12** gave the cis product **16** as the major component of a 1.6:1 mixture when subjected to TFA and light

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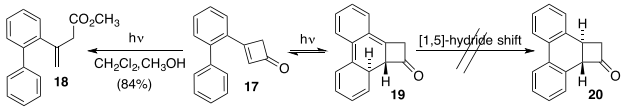
and exclusively gave *trans*-**16** in the absence of acid.[17] As with the pyrazines, we believe that the rate of the [1,5]-hydride shift is dictating the product formation here; substrates like biphenylpyridones or pyridine **11** undergo a relatively fast hydride shift and appear to not be susceptible to protonation, at least under the TFA conditions. Our results also suggest that having a nitrogen atom proximal to the benzylic carbon undergoing protonation was important for the generation of the cis product. We are currently examining other heteroaromatic substrates with the goal of gaining a better understanding of this phenomenon.

Finally, in an effort to determine whether acid could be used to intercept photoelectrocyclization intermediates with other "challenged" substrates, we examined the effect of acid on the photoelectrocyclization of cyclobutenone **17**. As illustrated in Scheme 3, when **17** was exposed to light in the absence of acid

Scheme 3. Attempted Cyclobutenone Photoelectrocyclizations

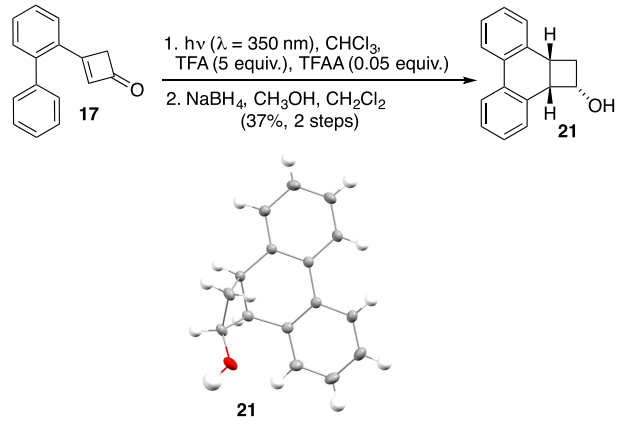


and the presence of methanol it did not undergo the photoelectrocyclization, [1,5]-hydride shift sequence but instead decomposed to ring-opened ester **18**.[18] We propose that the reason for the lack of photoelectrocyclization products from the reaction of **17** was a consequence of the [1,5]-hydride shift from **19** being energetically unfavorable as a result of it leading to the generation of trans-fused cyclobutanone **20**.

If our hypothesis about the reactivity of **17** was correct, then we imagined that we might be able to isolate the photoelectrocyclization product by capturing **19** with a proton. To our delight, when **17** was exposed to 350 nm light and a mixture of 5 equiv of TFA and 0.05 equiv of TFAA, we isolated cis-fused dihydrophenathrene **21** in 37% yield after reducing the relatively unstable cyclobutanone electrocyclization product immediately after its generation (Scheme 4).[19] This experiment shows that the protonation of the photoelectrocyclization intermediate may be a general phenomenon, especially for substrates whose [1,5]-hydride shift is relatively slow.

In summary, we have demonstrated that a combination of Suzuki−Miyaura coupling and photoelectrocyclization reactions leads to the efficient synthesis of heteroaromatic-containing dihydrophenanthrenes. Over the course of these studies, we have demonstrated that substitution can have a dramatic impact on the stereoselectivity of the reaction and that those electrocyclization intermediates that do not undergo a ready [1,5]-hydride shift can be intercepted through protonation.

Scheme 4. Acid-Mediated Photoelectrocylization of Cyclobutenone



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03214.

Experimental protocols and spectral data for all compounds (PDF)

Accession Codes

CCDC 1952750−1952752 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rainier@chem.utah.edu.

ORCID

Jon D. Rainier: 0000-0003-4386-2463

Notes

The authors declare no competing financial interest.

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(16) For example, whereas the structure of **2** would track with virulence inhibitors, **3** can be mapped onto the morphinan architecture. See ref 12 and Hudlicky, T. Recent advances in process development for opiate-derived pharmaceutical agents. *Can. J. Chem.* **2015**, *93*, 492−501.

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(18) In the absence of methanol, the ketene intermediate could be observed spectroscopically, but it eventually decomposed to unrecognizable material.

(19) We believe that TFAA reacts with small quantities of H_2O present in the reaction mixture. In the absence of TFAA, our yields for the reaction were capricious.

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